## REMARKS

Summary of Substance of Interview

On November 20, 2007, Applicants' representative, Anne J. Collins, Esq., contacted the Examiner by telephone to discuss the statutory rejection of claims 45-52 and 56-61 under 35 U.S.C. § 101, which the Examiner refers to on page 3 of the instant Office Action. In particular, Ms. Collins stated that she believed the rejection was made in error. The Examiner agreed that the rejection was made in error and stated that she would issue an Interview Summary to clarify the error.

Accordingly, an Interview Summary on Form PTOL-413 was mailed from the U.S. Patent and Trademark Office on December 3, 2007. In the Interview Summary, the Examiner states that "[a]fter reviewing the Action, Examiner conceded that the statement, 'the statutory rejection under 35 U.S.C. §101 of claims 45-52 and 56-61 as claiming the same invention as that of claims 35, 37-45 and 48-51 of US Patent No. 6,737,066 B1 is maintained until Applicant cancells [sic] or amends the conflicting claims so they are no longer coextensive in scope' is false" and that the "Examiner never intended to write this rejection" (Interview Summary, page 1).

Applicants thank the Examiner for clarifying the rejection.

Claim Objections

Claim 5 is objected to "because it is drawn in part to nonelected inventions and it depends from a rejected claim" (Office Action, page 2).

Applicants note that pending Claim 1 is a genus claim that links the different inventions (*i.e.*, sixty-three sequences) recited in Claim 5. MPEP 809.03 states "Where the requirement for restriction in an application is predicated upon the nonallowability of generic or other type of linking claims, applicant is entitled to retain in the case claims to the nonelected invention or inventions" (see MPEP 809.03, Eighth Ed., Aug. 2006 Rev., page 800-55). Accordingly, Applicants are entitled to retain Claim 5 in its present form in this application. Applicants will address the objection to Claim 5 upon an indication of allowable subject matter.

Affidavit under 37 C.F.R. § 1.132

The Examiner states that the "Mackett declaration under 37 CFR 1.132 filed on 06 September 2007 . . . fails to set forth any facts" and "includes statements which amount to an affirmation that the affiant has never seen the claimed subject matter before"(Office Action, page 2). The Examiner further states that the Mackett declaration "is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716." (Office Action, page 2). The Examiner asserts that "Dr. Mackett's opinion that a non-replicating or replication-impaired virus is not expected to be effective is not germane to the rejection at issue" (Office Action, page 2).

Applicants respectfully disagree. MPEP 716.01(c)(III) clearly states "[a]lthough factual evidence is preferable to opinion testimony, ***such testimony is entitled to consideration and some weight*** so long as the opinion is not on the ultimate legal conclusion at issue" (page 700-288; emphasis added).

The Declaration of Dr. Mackett under 37 C.F.R. § 1.132 was proffered to show that it was the opinion of one of skill in the art at the time of the invention that "it was ***generally accepted*** that replication competent viral vectors were required to provide effective and long lasting immunity" and that "[T]his belief was based on the expectation that a replication competent virus would produce more antigen in the host compared to a non-replicating or replication impaired virus" (Declaration, paragraph 4; emphasis added).

These statements, which are the opinions of a representative authority who was working in the field to which the invention pertains at the time of the invention, indicate that there was a clear bias in the art at that time towards using replicating viral vectors for immunization to ensure that a sufficient amount of antigen is produced. In light of this bias, one of skill in the art would not have been motivated to experiment with immunization using non-replicating or replication impaired viral vectors, which were not expected to express an adequate amount of antigen to provide effective immunity, to generate a CD8+ T cell immune response in a mammal against at least one target antigen, and would not have had a reasonable expectation of success in doing so.

Contrary to the Examiner's statement that the Mackett Declaration "is not relevant to the issue of nonobviousness of the claimed subject matter" and that "Dr. Mackett's opinion that a

non-replicating or replication-impaired virus is not expected to be effective is not germane to the rejection at issue," the statements in Dr. Mackett's Declaration speak to the extent to which one of skill in the art would have been motivated to substitute the replicating vaccinia virus vector in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* These statements are germane to the rejection at issue because the rejection was predicated, in part, on the Examiner's assertion that one of ordinary skill in the art would have been motivated to substitute the replicating vaccinia virus vector in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al* because "Sutter *et al.* clearly provides motivation for one skilled in the art to substitute a recombinant vaccinia virus with the replication-impaired vaccinia virus, MVA, because of its safety in mammals yet high efficiency in expressing foreign proteins in human cells (page 10847)" (Office Action, page 7). Thus, Dr. Mackett's Declaration warrants consideration and, as an opinion of a representative authority who was working in the field to which the invention pertains at the time of the invention, should be accorded considerable weight.

Double Patenting

The Examiner states that the "statutory rejection under 35 U.S.C. § 101 of claims 45-52 and 56-61 as claiming the same invention as that of claims 35, 37-45 and 48-51 of US Patent No. 6,737,066 B1 is maintained until Applicant cancels or amends the conflicting claims so they are no longer coextensive in scope" (Office Action, page 3).

As discussed above under "Summary of Substance of Interview," the statutory rejection of claims 45-52 and 56-61 under 35 U.S.C. § 101 was made in error. Thus, the rejection should be withdrawn.

Applicants thank the Examiner for acknowledging that the double patenting rejection of Claims 1-6, 10, 14-16, 27 and 31-33 as being unpatentable over claims 1, 2, 5-7, 15-18, and 20 of U.S. Patent No. 6,663,871 "will be withdrawn upon Applicants' submission of a compliant terminal disclaimer" (Office Action, page 3).

Applicants also thank the Examiner for acknowledging that the provisional nonstatutory double patenting rejections of Claims 1-3, 6, 7, 10, 12, 14 and 15 as being unpatentable over claims 1, 4, 5, 9, 11, 13, and 14 of copending Application No. 10/833,439 and over claims 1, 4,

5, 9, 11, and 13-16 of copending Application No. 10/833,744; Claims 1-3, 5-7, 10, 12, 14 and 15 as being unpatentable over claims 1, 4, 5, 9, 11, and 13-15 of copending Application No. 10/833,745; and of Claims 1, 6 and 27 as being unpatentable over claims 1-5 and 6-8 of copending Application No. 10/653,624 "are held in abeyance until allowable subject matter is determined" (Office Action, page 3).

Rejection of Claims 1-4, 6, 7, 10, 12, 14-16, 27, 28, 32 and 33 under 35 U.S.C. § 103(a)

Claims 1-4, 6, 7, 10, 12, 14-16, 27, 28, 32 and 33 are rejected under 35 U.S.C. § 103(a) "as being unpatentable over Li *et al.* (1993, reference No. AU4 in IDS filed on 06 July 2004) in view of Sutter *et al.* (1992, reference No. C52 in IDS filed on 09 November 2006) and Stoute *et al.* (1997, January)" (Office Action, page 4). The Examiner states that "Applicants' argument regarding the particular order of priming with an influenza virus and boosting with a recombinant vaccinia virus (rVV) is not germane to the rejection at issue" (Office Action, page 6) and that the "mere 'synergistic effect' does not prevent one skilled in the art from modifying Li's immunization method for improved safety in human" (Office Action, page 7). The Examiner also states that "Sutter *et al.* clearly provides motivation for one skilled in the art to substitute a recombinant vaccinia virus with the replication-impaired vaccinia virus, MVA, because of its safety in mammals yet high efficiency in expressing foreign proteins in human cells (page 10847)" (Office Action, page 7). The Examiner further states that "Applicants' assertion that the opinion of those of skill in the art, including Dr. Mackett's declaration, is that an immune response requires a replication-competent virus is not germane to the rejection at issue" (Office Action, page 7). According to the Examiner, "the combination of Sutter *et al.* and Li *et al.* is properly motivated and a *prima facie* case of obviousness is properly established" (Office Action, page 7).

Applicants respectfully disagree. Applicants maintain that the combined teachings of Li *et al.* and Sutter *et al.* fail to teach or suggest that one of skill in the art should replace the replicating vaccinia virus in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* In particular, Applicants submit that the teachings in Li *et al.* regarding the "remarkable synergistic effect" achieved using the specific combination of a recombinant influenza virus prime and replicating recombinant vaccinia virus boost would sufficiently discourage one of skill

in the art from modifying the method of Li *et al.* by replacing the replicating vaccinia virus in the boosting composition with an alternative vector, such as the MVA vector of Sutter *et al.*

Applicants would like to clarify that Applicants' remarks in the Amendment filed on September 6, 2007 concerning the teaching in Li *et al.* that the reverse order of administration of the recombinant influenza and vaccinia virus vectors failed to induce protective immunity, were not intended to imply that the Examiner suggested reversing the order of the vectors in the method of Li *et al.* Rather, these remarks were included because they support the argument that the teachings in Li *et al.* actually discourage one of skill in the art from modifying their immunization method by replacing the recombinant vaccinia virus with an alternate vector. For example, when Li *et al.* modified their method by reversing the order of the vectors, the modified method failed to induce protective immunity, and the synergism of the vectors was destroyed. Applicants submit that replacing the replicating recombinant vaccinia virus in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* is an even more drastic modification to the method of Li *et al.* than simply reversing the order of the vectors. Therefore, based on the results presented in Li *et al.*, one of skill in the art would reasonably expect that substituting the replicating recombinant vaccinia virus in the method of Li *et al.* with an MVA vector would eliminate the synergism achieved by the specific combination of a recombinant influenza virus prime and replicating recombinant vaccinia virus boost.

Sutter *et al.* do not teach or suggest that immunization with their MVA vector can elicit a CD8+ T cell response in a mammal. Therefore, Sutter *et al.* do not provide a reasonable expectation of success in eliciting a CD8+ T cell response in a mammal by incorporating their MVA vector into the immunization method of Li *et al.*

Although Sutter *et al.* teach that recombinant MVA "were able to synthesize high levels of a foreign protein in human cells" (Sutter *et al.*, page 10847, right column), one of skill in the art would recognize that this result was based on an *in vitro* experiment in which Sutter *et al.* used a high titer of virus (*i.e.*, 15 plaque forming units (pfu) of either MVA or replicating Western reserve strain vaccinia virus per cell) to infect cells in tissue culture (Sutter *et al.*, paragraph bridging pages 10848-10849). Because the MVA and the replicating vaccinia virus employed by Sutter *et al.* produce similar amounts of protein on a pfu for pfu basis, one of skill in the art would expect these viruses to express equivalent levels of protein in the *in vitro* assay

of Sutter *et al.* on account of the high titer of virus used to infect the cells. The high titer of virus used in the *in vitro* expression experiments of Sutter *et al.* renders the replicative characteristics of the respective viruses moot, because the infected cells are overwhelmed with virus. Thus, the results obtained from this assay cannot be extrapolated to *in vivo* immunization, for which a much lower titer of virus is typically used, and the replicative ability of the virus plays a major role in determining the expression levels of viral genes (see Reference AT8 of record (Watson *et al.*), page 57, right column). Accordingly, upon considering the teachings of Sutter *et al.* as whole, one of skill in the art would not conclude that the *in vitro* expression results of Sutter *et al.* correlate with MVA gene expression *in vivo*. Thus, one of skill in the art would not replace the replicating vaccinia virus of Li *et al.* with the MVA vector of Sutter *et al.* based on the expression data presented in Sutter *et al.*

Regarding the Examiner's assertion that "Sutter *et al.* clearly provides motivation for one skilled in the art to substitute a recombinant vaccinia virus with the replication-impaired vaccinia virus, MVA, because of its safety in mammals," Applicants note that the suggestion by Sutter *et al.* that MVA has "potential . . . to serve as an exceptionally safe" vector (Sutter *et al.*, page 10847, right column) is not supported by clinical or other experimental data demonstrating that MVA is safe for *in vivo* applications. Furthermore, the mere suggestion that MVA is "exceptionally safe" does not compensate for the failure of Sutter *et al.* to provide a reasonable expectation that immunization with MVA could successfully generate a CD8+ T cell response against a target antigen in a mammal. Accordingly, one of skill in the art would not replace the replicating vaccinia virus of Li *et al.* with the MVA vector of Sutter *et al.* based on mere speculation by Sutter *et al* that MVA is safe.

Applicants respectfully disagree with the Examiner's remarks that "Applicants' assertion that the opinion of those of skill in the art, including Dr. Mackett's declaration, is that an immune response requires a replication-competent virus is not germane to the rejection at issue" (Office Action, page 7). As discussed above, the statements in the Declaration of Dr. Mackett under 37 C.F.R. § 1.132 are germane to the rejection at issue because they are the opinion of a representative authority who was working in the field to which the invention pertains at the time of the invention, and speak to the extent to which one of skill in the art would have been motivated to substitute the replicating vaccinia virus vector in the boosting composition of Li *et*

*al.* with the MVA vector of Sutter *et al.* Because the rejection at issue was predicated, in part, on the Examiner's assertion that "Sutter *et al.* clearly provides motivation for one skilled in the art to substitute a recombinant vaccinia virus with the replication-impaired vaccinia virus, MVA, because of its safety in mammals yet high efficiency in expressing foreign proteins in human cells (page 10847)" (Office Action, page 7), Dr. Mackett's Declaration warrants consideration and, as an opinion of a representative authority who was working in the field to which the invention pertains at the time of the invention, should be accorded considerable weight.

To lend additional weight to the opinions expressed by Dr. Mackett in the Declaration, Applicants previously cited reference AT8 of record, which teaches that those of skill in the art were of the opinion that "[t]o elicit an adequate immune response, ***live vaccine virus must replicate*** within the recipient" (Reference AT8, page 57, right column; emphasis added). This teaching is consistent with, and corroborates, the views expressed by Dr. Mackett in the Declaration.

Clearly, the combined teachings of Li *et al.* and Sutter *et al.* do not suggest substituting the replicating vaccinia virus vector in the boosting composition of Li *et al.* with the MVA vector of Sutter *et al.* because:

1) Li *et al.* teach the "remarkable synergistic effect" of using the specific combination of a recombinant influenza virus prime and replicating recombinant vaccinia virus boost in their immunization method to induce CD8+ T cell-mediated protective immunity against malaria;

2) Sutter *et al.* do not teach or suggest that immunization with their MVA vector can elicit a CD8+ T cell response in a mammal;

3) Sutter *et al.* fail to demonstrate that MVA is able to synthesize high levels of a foreign protein *in vivo* in human cells, or that MVA can be safely used to immunize humans or other mammals; and

4) the Mackett Declaration and the teachings of Reference AT8 indicate that there was a clear bias in the art at the time of the invention towards using replicating viral vectors for immunization.

Stoute *et al.* do not provide the teaching that is lacking in the Li *et al.* and Sutter *et al.* references that would render Applicants' claimed invention obvious. At most, the teaching in Stoute *et al.* that "[s]trong adjuvants were required" in their vaccine to protect "adults who have

never been exposed to malaria against experimental challenge with *P. falciparum*" (Stoute *et al.*, page 90, column 1) would have directed one of skill in the art to use an adjuvant (*e.g.*, the SBAS2 adjuvant of Stoute *et al.*) in either the heterologous prime-boost method of Li *et al.*, or the MVA vector immunization of Sutter *et al.* Stoute *et al.* clearly do not provide a teaching that links the teachings of Li *et al.* and Sutter *et al.*

For the reasons discussed above, the combination of Li *et al.*, Sutter *et al.* and Stoute *et al.* do not teach or suggest Applicant's claimed methods of generating a CD8+ T cell immune response in a mammal against at least one target antigen.

Thus, the combined teachings of Li *et al.*, Sutter *et al.*, and Stoute *et al.* clearly do not render Applicants' claimed invention obvious.

Fifth Supplemental Information Disclosure Statement

A Fifth Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested. Copies of the cited references, AT9, AS10-AU10, and C37-C39, were submitted with Information Disclosure Statements (IDSs) that were previously filed, and fully considered and acknowledged, in this application (see IDSs filed on July 6, 2004, October 28, 2004 and November 9, 2006, and Office Actions dated July 5, 2006 and April 2, 2007). In order to comply fully with 37 C.F.R. §§ 1.97 and 1.98, citations for these references on the attached Listing of References have been revised to include dates, which were lacking in the earlier-filed IDSs.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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